DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administratio

Dallas District
4040 North Central Expressw
Dallas, Texas 75204-3145

04-DAL-WL-07

November 7, 2003

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Marshall G. Cothran, CEO
Central Texas Regional Blood and Tissue Center
4300 North Lamar Boulevard
Austin, TX 78756-3421

Dear Mr. Cothran:

The Food and Drug Administration (FDA) conducted an inspection of your firm, Central Texas Regional Blood and Tissue Center located in Austin, Texas, from August 4 through September 8, 2003. During the inspection, the FDA investigators documented violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) and Title 21, Code of Federal Regulations (21 CFR) Parts 600-680. Listed below are certain serious violations that reveal problems with your firm's Good Manufacturing Practices (GMP). We did not list all of your firm's violations. These violations represent observations noted on the Form FDA-483 issued at the conclusion of the inspection.

1. Your firm failed to defer from further donations of human blood and blood components donors who had a reactive screening test for evidence of infection due to a communicable disease agent [21 CFR 610.40(h)(1)].

   Specifically, one donor tested Nucleic Acid Test (NAT) HIV positive on a unit donated 4/4/2002. The donor donated a Whole Blood unit on 4/16/2002. The testing laboratory requested the Fresh Frozen Plasma (FFP) to be tested from the 4/16/2002 donation and all tests were negative including the NAT HIV. The donor was deferred for 6 months until 10/2002 and returned for re-testing for HIV at that time. The laboratory sample drawn 10/2002 was non-reactive for Anti-HIV1/2, HIV antigen, NAT HIV, and NAT HCV. The donor was re-entered and listed as eligible to donate 11/2002. Products donated since re-entry are one Whole Blood and seven apheresis units. Five apheresis units were distributed. At this time, FDA has no re-entry algorithm for donors having tested positive by NAT for HIV. This donor was not permanently deferred in your firm's [redacted] computer system.

One donor had a reactive EIA test for HIV-1 on 10/4/1991 and tested Western Blot (WB) negative on 10/11/1991. The donor was not deferred in the old [redacted] or current [redacted] computer systems and continued to donate 8 units of blood under your firm's "Silent Re-entry Program." These units were not distributed. During a donor merge, it was discovered that this donor should be permanently deferred, and the donor was deferred on 7/29/2002. Another donor had a reactive EIA test for HIV1/2 on 4/28/1994 and WB Indeterminate on 5/9/1994. This donor was accepted for donation on 5/7/1998. The components for this unit were destroyed and the donor has not donated since. This donor was not permanently deferred in the [redacted] computer system.

Two donors had a reactive test for HCV. One donor was permanently deferred in the previous [redacted] computer system but the donor later registered under another name and was not deferred in the current [redacted] system. The donor was accepted and donated 11/1999 and 12/2001. Components from 11/1999 were distributed and one of the components was transfused. The error was discovered and the donor was deferred 1/2003. The second donor tested reactive for HCV on a single antigen, unlicensed test in May, 1990 and was permanently deferred. After additional testing was done on a sample drawn in July, 1990 and was negative, the donor was listed as eligible to donate. When further guidance was issued by FDA in 1991 regarding donors that had tested positive for HCV, the donor was permanently deferred. This donor returned in November 2002 and a sample of blood was drawn and tested for HCV 3.0 EIA for re-entry. The donor was non-reactive by this test but no RIBA 3.0 supplemental testing was performed on the sample as required and the donor was re-entered in December 2002 by the Donor Counselor. This donor has donated three units of blood on 2/2003, 6/2003, and 8/2003. This donor was not permanently deferred in the [redacted] system.

Another donor tested reactive 8/6/2001 for HBsAg and negative for Anti-HBc. The donor was permanently deferred on 8/6/2001 but the deferral was removed 8/10/2001 by the Donor Counselor. The donor returned 8/10/2001 and donated an apheresis unit. In addition, the donor returned to donate a Whole Blood unit on 8/16/2001. The apheresis unit and components from the Whole Blood unit were distributed. The donor was re-entered before the required minimum eight week wait time which is the time period recommended in the December 2, 1987 FDA Memorandum on the management of donors initially reactive for HBsAg.

Two donors tested reactive for Anti-HBc. Although the donations by these donors were for autologous units, neither donor was permanently deferred in the [redacted] computer system to prevent subsequent allogeneic donations.

2. Your firm failed to defer donors who had a history of viral hepatitis after their 11th birthday [21 CFR 640.3(c)(1)].

   Our investigators documented 3 donors who had been previously permanently deferred because of a history of viral hepatitis after age 11 but the permanent deferral was removed by either the Donor Counselor or the Medical Director without a complete investigation to determine if the removal of the permanent deferral met donor re-entry qualifications. One donor with a previously reactive viral marker test for hepatitis was accepted based only on the testing of a blood sample by screening tests for the viral marker of hepatitis. The two donors who answered "Yes" to "have you ever had yellow jaundice, liver disease, viral hepatitis, or a positive test for hepatitis" were accepted because the Medical Director contacted both the donors and determined that both donors were eligible to donate because one was asymptomatic for hepatitis associated with treatment of dengue fever and the other one had hepatitis associated with mononucleosis. All three donors have donated blood and the components have been distributed.

3. Your firm used human blood and blood components from donors who had not been shown to be suitable by a re-qualification method or process found to be acceptable for such purposes by FDA after such donors had previous records of a reactive screening test for evidence of infection due to a communicable disease agent [21 CFR 610.40(h)(1)].

   Specifically, one donor tested NAT HIV positive on a unit donated 4/4/2002. The donor donated a Whole Blood unit on 4/16/2002. The testing laboratory requested the FFP to be tested from the 4/16/2002 donation and all tests were negative including the NAT HIV. The donor was deferred for 6 months until 10/2002 and returned for re-testing for HIV at that time. The laboratory sample drawn 10/2002 was non-reactive for Anti-HIV1/2, HIV antigen, NAT HIV, and NAT HCV. The donor was re-entered and listed as eligible to donate 11/2002. Products donated since re-entry are one Whole Blood and seven apheresis units. Five apheresis units were distributed. At this time, FDA has no re-entry algorithm for donors having tested positive by NAT for HIV. This donor was not permanently deferred in your firm's [redacted] computer system.

One donor tested reactive for HCV on a single antigen, unlicensed test in May, 1990 and was permanently deferred. After additional testing was done on a sample drawn in July, 1990 and was negative, the donor was listed as eligible to donate. When further guidance was issued by FDA in 1991 regarding donors that had tested positive for HCV, the donor was permanently deferred. This donor returned in November 2002 and a sample of blood was drawn and tested for HCV 3.0 EIA for re-entry. The donor was non-reactive by this test but no RIBA 3.0 supplemental testing was performed on the sample as required and the donor was re-entered in December 2002 by the Donor Counselor. This donor has donated three units of blood on 2/2003, 6/2003, and 8/2003 and two of these units were distributed. This donor was not permanently deferred in the [redacted] system at the time of the inspection.

Another donor tested reactive 8/6/2001 for HBsAg and negative for Anti-HBc. The donor was permanently deferred on 8/6/2001 but the deferral was removed 8/10/2001 by the Donor Counselor. The donor returned 8/10/2001 and donated an apheresis unit. In addition, the donor returned to donate a Whole Blood unit on 8/16/2001. The apheresis unit and components from the Whole Blood unit were distributed. The donor was re-entered before the required minimum eight week wait time which is the time period recommended in the December 2, 1987 FDA Memorandum on the management of donors initially reactive for HBsAg.

4. Your firm failed to maintain complete and accurate records from which unsuitable donors could be identified so that products from such individuals would not be distributed [21 CFR 606.160(e)] and records to identify the person performing the work so to provide a complete history of the work performed [21 CFR 606.160(a)(1)].

Specifically, when the investigators requested a search of some of the various donor permanent deferral codes in your [redacted] database, 72 donors had various permanent deferral codes entered into the "Comment" field but these donors did not have a permanent deferral status entered into the "Deferral Code" field of the [redacted] database. The "Comment" field is not referenced for identification of permanently deferred donors. Out of 72 donors, 10 were verified to meet the criteria for permanent deferral.

Duplicate donor information is not always captured at time of donor registration. Six QIRs generated involved duplicate donors and two of these duplicate donors were permanently deferred but donated under a different

name. One donor was deferred because of HCV Unconfirmed and the other was for cancer. Components from these donors were distributed.

Laptop computers that are used for registration of donors on a mobile blood drive are downloaded with the donor deferral list from the [redacted] computer system. The laptop computers search for "last name" only and the donor last name is variable. The laptop computer does not cross reference any additional information for duplicate donors such as date of birth or social security number. The investigators found ten QIRs that were initiated for deferred donors who were accepted for donation on mobile drives.

In addition, your SOP "Encountering Deferred Donors" does not require the documentation of the person(s) removing donor deferral codes(s). A donor was incorrectly entered into the [redacted] system with a deferral status of temporary deferral (TP) for low hematocrit (HCT) and a permanent deferral code for CJD instead of for low HCT. The [redacted] system automatically removed the TP when the temporary deferral time had past but the permanent deferral code for CJD remained in the system. Later the code for CJD was removed but you were unable to identify the person who removed this code or why it was removed.

5. Your firm failed to maintain written standard operating procedures including all steps to be followed in the collection and processing of blood and blood components for transfusion and further manufacturing purposes [21 CFR 606.100(b)]. For example:

As the result of clotted unit complaints, you notified FDA that your corrective action included a revised component procedure for processing "long draw units". Then you notified FDA that the corrective action would be to revise the "hand off" process between the donor room and processing with a chain of custody formed. As of this inspection, these revisions have not been made or implemented. This observation was also made during the FDA inspection of June 2002.

Your SOP "Leukocyte Reduction Filtration System for Red Blood Cells for [redacted] for leukocyte reduction has not been revised to include the current processing steps for labeling, discarding the bag after filtration, and the use of a sample bag instead of segments for the collection of quality control samples.

The SOP "Vital Signs/Physical Examination Standard Operation Procedure" for taking vitals signs of the donor is not specific as to how many times the

vital signs can be taken and does not require each vital sign taken to be recorded.

When your firm re-attached satellite bags to Whole Blood units by the sterile docking device, the satellite bag unit number did not correspond to the Whole Blood unit number. This was discovered by your consignee. You implemented an informal policy that only one unit can be sterile docked at a time but your SOP has not been revised to include this step. This observation was made by the investigators during the current FDA inspection as well as the FDA inspection in June 2002.

6. Your firm failed to submit Biological Product Deviation Reports within the 45-calendar days as required in 21 CFR 606.171(c). During the time period from April 2002 to April 2003, 25 out of 92 Biological Product Deviation Reports (BPDR) were submitted after 45 days. Eight BPDRs were less than 60 days with the remaining number ranging from 60 to 272.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure that all blood and blood components produced and issued by your blood bank are in compliance with the Act and the cGMP regulations. You should take prompt action to correct these violations. Failure to correct these violations may result in administrative and/or regulatory action without further notice. Such action includes license suspension and /or revocation, seizure and/or injunction.

We received your October 14, 2003 response to the FDA 483, Inspectional Observations that the FDA investigators issued at the conclusion of the most recent inspection of your firm. We have completed our review of your response and have determined that your response is inadequate to address all the violations that FDA documented at your firm. Our evaluation follows and is numbered or labeled to correspond to the items as they appeared on the FDA-483 and in your response:

Items: 1a, 4b,c, 6c: The response appears to be adequate to address the duplicate donor records and the enhancement of the laptop Access database. However, the response did not propose corrective action or include procedural changes to ensure the accuracy of the information given the consignee and /or the FDA. The example of the incorrect information in the notification was the donor that was confirmed negative for HCV and was eligible for re-entry when no confirmation test was ever performed.

Item 1b: Your response is inadequate to address the noted observation. You state that there has never been a "silent re-entry" program for donors at your firm but the SOP for Serology Deferrals in effect 8/90 gives the directions that donor samples testing repeatable reactive for RPR, HIV, HTLV I, and HBsAg will be further tested by confirmation tests. Donor units testing confirmation negative will be technically discarded and no donor notification will take place. These donors were not permanently deferred but were allowed to continue to donate for donor relationship reasons because of the policy of your firm's COO in 1990. The code for the positive testing was noted in the comments section enabling the donor to be identified and the units discarded but no permanent deferral code was entered. Both this policy and the current policy in place is explained and dated 8/2002 in the QIR 2002-362 documentation. However, you do not address how you plan to assess how many donors may still be in this category and still not permanently deferred in the present [redacted] system.

Items f,g,h: The response is inadequate to address the noted observations. You state under the system corrective action that the [redacted] computer system automatically defers all donors when reactive screening infectious disease testing results is received. These donors had positive screening infectious disease tests and had not been entered into the previous [redacted] system as permanent deferrals so when they were transferred to the current [redacted] system, they were not permanently deferred. Two of the donors gave autologous units. Other donors may still not be deferred in the new [redacted] system. In addition, how is your firm going to implement controls so deferred donors can donate autologous units and still ensure that these donors will remain deferred? These controls would also apply to donors who would be permanently deferred for other reasons other than reactive screening infectious disease tests.

Items 1c,d,e, 3a,b,c, 4a, 16a: The response is inadequate to address the noted observations. You state that no re-entry of donors with positive test results will be allowed with the exception of Syphilis effective August 22, 2003; however, you do not present as corrective action what steps you will take to ensure that the Donor Counselor does not continue to change the donor status and re-enter donors. You do not state how you will ensure that all donors that have various deferral codes in the comment section in the [redacted] system will be evaluated to meet the criteria for permanent deferral in the [redacted] system in addition to the 72 that were found during the inspection, but instead you intend to review these same reports that were generated during the current inspection from the donor deferral database that the FDA investigators requested during the inspection.

Items 2a,b,c: The response is inadequate to address the noted observations. Although these donors were previously deferred, both the Donor Counselor and the Medical Director re-entered these donors without the proper investigation and documentation to substantiate that these donors did not have viral hepatitis of any origin after age 11. The regulation does not distinguish between viral hepatitis A,B,C,E, etc. or viral hepatitis caused from other diseases such as mononucleosis and CMV. The regulation, 21 CFR 640.3(c)(1), simply states that if an individual has a history of viral hepatitis after their 11th birthday, the person cannot donate Whole Blood. The proposed corrective action does not provide further assurance that the problem will not recur.

Items 8a,b, 9, 12b: The response appears to be adequate to address the noted observations; however, the failure to maintain written SOPs including all steps to be followed continues to be an observation from the current inspection as well as the inspection of June 2002. In your response under system corrective action to outstanding Requests for Deviations to SOPs, you state that the goal is to streamline the system and implement SOPs in a more timely fashion, however, you continue to have approved revisions of SOPs that have not been implemented and you have been unable to meet the timelines your firm has set for this process.

Items 8c,15: The response appears to be adequate to address the noted observation.

Item 14: The response appears to be adequate to address the noted observation; however, the system that you plan to develop to monitor the status of reportable BPDRs can only be fully evaluated after implementation takes place.

Item 17: We have determined that the response is inadequate to address the noted observation. In your response you give the background stating that the [redacted] computer system keeps an internal audit trail when a permanent deferral is removed by a person and if the deferral is temporary, the [redacted] computer system removes the deferral automatically when the deferral time has past. In addition, you state the SOP [redacted] does not deal with removing deferrals so does not document a requirement for identifying the person removing the deferral. Your system corrective action states that no internal audit trail is necessary for automatic removal of a temporary deferral by the [redacted] system because the identification of the person who performs the succeeding registration that causes the deferral to be removed is recorded on the Donor Record. However, during the FDA inspection, you

were unable to produce documentation to identify the person who removed the permanent deferral that is not automatically removed by the [redacted] system. You did not address this in your system corrective action part of the response.

We request that you notify this office in writing, within fifteen (15) working days of the receipt of this letter, of the specific steps you have taken to correct these violations, including examples of any documentation showing that corrections have been achieved. If you cannot complete all the corrections before you respond, please explain the reason for your delay and the date by which each item will be corrected and documented.

Please send your reply to the Food and Drug Administration, Attention: Carolyn A. Pinney, Compliance Officer, at the above letterhead address. If you have any questions regarding any issue in the letter, please contact Carolyn A. Pinney at (214) 253-5312.

Sincerely,

Reynaldo R. Rodriguez, Jr.
for Michael A. Chappell
Dallas District Director